REMARKS

I. Status of the Claims

Claims 1-11, 13-26 are currently pending. Claims 12, 27-47 were withdrawn by the Examiner from consideration on their merits for allegedly being directed to non-elected species. Claims 13, 19-21, and 23 are cancelled without prejudice or disclaimer. Claims 1-3, 14, and 22 were amended to further clarify the invention. Support for amendments can be found, for example, on page 9, second paragraph; page 23, line 8 to page 24, line 22; and page 29, last paragraph to page 31, first paragraph. No new matter has been introduced into the application as a result of the present amendments.

II. Priority

Applicants acknowledge Examiner's withdrawal of previous objection to Applicants' priority claim to provisional application 60/406,662, which was filed on September 6, 2002. Examiner found that the provisional application cites working examples that support the pending claims.

III. Withdrawal of Previous Objections to the Specification and Claims

Applicants acknowledge Examiner's withdrawal of previous objections to the specification for containing a hyperlink. Applicants also acknowledge Examiner's withdrawal of previous objections to claims 7-8, 14, and 16 for improper dependency.

IV. Withdrawal of Previous Rejections to Claims 11 and 21 Under 35 U.S.C. §112, Second Paragraph

Applicants acknowledge Examiner's withdrawal of previous rejections to claims 11 and 21 for allegedly being indefinite.

V. Double Patenting

Claims 1-5, and 13-26 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-5, 14, 43-45, 48-51, and 55-58 over U.S. Patent No. 7,083,911. Applicants traverse the rejection.

Applicants have nevertheless filed a terminal disclaimer, which is attached to the response. Applicants submit that the terminal disclaimer has obviated the rejection.

VI. Withdrawal of Previous Rejections to Claims 1-8, 19-20, and 22-26 under 35 U.S.C. §102(e)

Examiner acknowledges that Crouch et al. (U.S. Patent Appl. No. US2004/0253658) ("Crouch") does not teach a single composition comprising both a transferase-quenching reagent and the bioiluminescence-generating mixture. Therefore, the Examiner withdrew previous rejection under 35 U.S.C. §102(e) over Crouch. Applicants acknowledge Examiner's withdrawal of previous rejections under 35 U.S.C. §102(e)

VII. Claim Rejections under 35 U.S.C. § 103(a)

a. Claim rejection under 35 U.S.C. § 103(a) over Crouch

Claims 1-8, 19-26 stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Crouch. Specifically, the Examiner asserts that Crouch allegedly teaches allowing the transferase reaction to proceed for a period of time before adding luminogenic molecules, and adding a stopping solution before measurement. The Examiner refers to paragraph [0072] for the assertion that Crouch teaches many compounds other than EDTA, EGTA, or phosphoric acid that can be used as stopping agents. See page 8 of the Office Action. Applicants respectfully traverse the rejection. Claims 19-21 and 23 are now canceled. The cancellation has rendered the rejection moot with respect to claims 19-21 and 23.

The Supreme Court in Graham set out the factual inquiry, which the Patent Office must follow in determining obviousness. *Graham v John Deere Co.*, 383 U.S. 1, 17 (1966). The inquiry includes (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. Further, when applying §103 as set forth in *Graham v John Deere*, the following tenets of patent law must be adhered to:

(a) the claimed invention must be considered as a whole;

(b) the reference must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(d) Reasonable expectation of success is the standard with which obviousness is determined.

MPEP 2141 *Hoods v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for failing the Graham analysis.

(1) The scope and content of the cited art

Crouch merely relates to a method for measuring protein kinase activity which includes (a) providing a first solution of ATP and protein kinase and a second solution of ATP (control); (b) adding a kinase substrate to the first and second solutions to form reaction mixtures; and (c) measuring ATP or ADP concentration or the rate of change with time based on a bioluminescence reaction. See Abstract of Crouch. A separate stopping agent of phosphoric acid or metal chelators, if used at all, is added to the reaction mixture in step (b') to stop the reaction of the kinase prior to initiation of the bioluminescence reaction. See paragraph [0069].

(2) The differences between the prior art and the claims at issue

The invention, as presently claimed, is directed to bioluminescence-based methods for measuring transferase enzymatic activity. After initiating a transferase reaction, a single reagent is added to the transferase reaction mixture which stops the transferase reaction and initiates the bioluminescence reaction in one step. The single reagent includes a chemostable luciferase, a luminogenic molecule and a detergent. The chemostable luciferase is defined on page 23, line 8 to page 24, line 22 of the specification. The detergent selectively stops transferase activity without substantially affecting chemostable luciferase activity. See present claims 1-3.

As correctly pointed out by the Examiner, Crouch does not teach that the transferase stopping agent should be combined with the bioluminescence-generating mixture in a single composition. See page 6 of the Office Action. There is no disclosure

or suggestion in Crouch of a method that employs a single reagent which stops the kinase reaction and initiates the bioluminescence reaction in one step as presently claimed. A separate stop reagent of phosphoric acid or metal chelators, if used at all, is added to the reaction mixture in step (b') to stop the reaction of the kinase prior to initiation of the bioluminescence reaction. See paragraph [0069]. The use of a separate stop solution demands extra steps to be performed prior to initiating the bioluminescence reaction. See Crouch's Example 1 and paragraph [0102]. See also claims 53 and 55 of Crouch. In fact, not only is Crouch devoid of any teaching or suggestion of combining the steps of quenching transferase reaction and initiating luciferase reaction into one, Crouch declares it advantageous to separate the two actions into two steps. See paragraphs [0069][0072].

Moreover, Crouch does not teach the use of a detergent as a stopping agent. Crouch merely relates to the use of EDTA, EGTA or phosphoric acid to stop transferase activity. Contrary to Examiner's assertion, Crouch does not teach or suggest in paragraph [0072] that many compounds, other than EDTA, EGTA, or phosphoric acid, can be used as stopping agent. See page 8 of the Office Action. A general statement in paragraph [0070] that a number of acids such as phosphoric acid can be used as stopping agent, or a single example of using staurosporine does not teach or suggest detergents as stopping agents.

(3) The level of ordinary skill in the pertinent art

Crouch is at least of the level of ordinary skill in the art, yet it does not occur to her the use of detergent as stopping agent in conjunction with a chemostable luciferase. Further, there is nothing implicit in the knowledge of one of ordinary skill in the art to modify Crouch's teaching to combine the transferase quenching reagent with the bioluminescence mixture in one solution.

Thus, Crouch does not teach any desirability of the present invention. The present claims would not have been obvious to one of ordinary skill in the art over Crouch with a reasonable expectation of success.

Moreover, Applicants submit that the claimed invention is not obvious over Crouch because Crouch does not teach or suggest all the limitations of independent claims 1-3. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP 2143.03 (*citing In re*

Royka, 490 F.2d 981 (CCPA 1974)). Crouch does not teach or suggest a single regent comprising a detergent and a luciferase. Crouch does not teach using a detergent as the stopping agent, nor does it teach a chemostable luciferase. Thus, Crouch does not teach all limitations of the claims.

Based on the foregoing, Applicants submit that Crouch does not teach or suggest the claimed invention, or any desirability of the claimed invention. Accordingly, Applicants respectfully submit that the invention, as a whole, is not obvious over Crouch. Reconsideration and withdrawal of the rejection of pending claims 1-8, 22, and 24-26 under 35 U.S.C. § 103(a) in view of Crouch is respectfully requested.

b. Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Simpson

The Examiner further rejects Claims 1-8, 13-17, and 19-26 as allegedly being obvious over Crouch in view of Simpson et al. (J. Biolum. and Chemilum, 6:97-106, 1991) ("Simpson") Specifically, the Examiner asserts that Simpson studied the effects of various types of detergents on the kinetics of the luciferase/luciferin reaction. The Examiner alleged that it would have been obvious to one skilled in the art to use a secondary solution comprising luciferin, luciferase and a detergent in a method of detecting transferase activity as described by Crouch. Applicants respectfully traverse the rejection. Claims 13, 19-21, and 23 are now canceled. The cancellation of the claims has rendered the rejection moot with respect to claims 13, 19-21, and 23.

As discussed above, Crouch does not teach or suggest using a detergent for a stopping agent. Neither does Simpson. Thus, neither cited art recognize or appreciate the utility of detergents as stopping agents. Simpson merely relates to the effects of detergents on luciferase activity. Simpson, however, does not teach or suggest using a detergent to stop transferase activity. Simpson may have shown that some types of detergent inhibit luciferase activity, whereas other types of detergent might stimulate luciferase activity within a narrow range of detergent concentrations. See Table 1, and page 102, left column, first paragraph of Simpson. But even among detergents that appear to stimulate luciferase activity, the alleged stimulation is mitigated by the fact that some detergents also irreversibly destabilize and inactivate the luciferase enzyme. See for example, page 102, left column, Table 1, and Figure 2. Thus, Simpson teaches the variability and overall

negative effects of detergents on luciferase activities. Without any teaching in either Simpson or Crouch the utility of detergents as stopping agents, one of ordinary skill in the art would have avoided using detergent in an assay in which the transferase activity measurement ultimately depends on the luciferase activity. In view of the overall negative effect of detergents as shown in Simpson, a remote "possibility" or a mere suggestion to investigate is no motivation to one of ordinary skill in the art to combine Crouch with Simpson with a reasonable expectation of success. Thus, the claimed invention, as a whole, is not obvious over Crouch and Simpson.

Further, as discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Crouch does not teach the use of a detergent as stopping agent or a chemostable luciferase. Neither does Simpson. Thus, the cited art, even in combination, does not teach every element of the claims and does not arrive at the present invention.

Accordingly, Applicants respectfully submit that the Examiner failed to establish a *prima facie* case of obviousness over Crouch in view of Simpson. Withdrawal of the rejection of pending claims 1-8, 14-17, 22, and 24-26 under 35 U.S.C. §103(a) over Crouch in view of Simpson is in order and is respectfully requested.

c. Previous Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Briggs

Because the claims are allegedly deemed obvious over Crouch, the Examiner maintains previous rejections of claims 1-10, 19-20, and 22-26 as allegedly being obvious over Crouch in view of Briggs et al. (Biochem, 39:489-495, 2000, "Briggs"). Applicants respectfully traverse the rejection.

As discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Additionally, Crouch does not teach the use of a detergent as the stopping agent or a chemostable luciferase. Briggs adds nothing to Crouch that could remedy the deficiencies. Briggs merely relates to additional tyrosine kinase family members. A disclosure of tyrosine kinase family members is not a

teaching or suggestion of a method that employs a reagent that simultaneously quenches a transferase reaction and initiates the bioluminescence enzyme reaction as recited in the present claims. Further, Briggs does not teach or suggest the use of detergent as stopping agent, or a chemostable luciferase. The cited art, either alone or in combination, does not teach or suggest the desirability of the invention, nor does it teach every element of the claims. Accordingly, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) based on the combination of Crouch and Briggs is improper and should be withdrawn.

d. Previous Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Lev

Because the claims are allegedly deemed obvious over Crouch, the Examiner maintains previous rejections of Claims 1-8, 11, 19-20 and 22-26 as allegedly being obvious over Crouch in view of Lev et al. (EMBO J., 10:647-654, 1991, "Lev") Applicants respectfully traverse the rejection.

As discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Additionally, Crouch does not teach the use of a detergent as the stopping agent or a chemostable luciferase. Lev adds nothing to Crouch that could remedy the deficiencies in Crouch's teachings. Lev merely relates to additional tyrosine kinase family members. A disclosure of tyrosine kinase family members is not a teaching or suggestion of a method that employs a reagent that simultaneously quenches a transferase reaction and initiates the bioluminescence enzyme reaction as recited in the present claims. Further, Lev does not teach or suggest the use of a detergent as a stopping agent, or a chemostable luciferase. The cited art, either alone or in combination, does not teach the desirability of the invention, nor does it teach all elements of the claims. Accordingly, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) based on the combination of Crouch and Lev is improper and should be withdrawn.

VIII. Conclusion

The Applicants believe that the application is ready for allowance. A favorable decision is earnestly solicited. If the Examiner has any question, he is invited to call the undersigned attorney at 312-913-3303.

Respectfully submitted,

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